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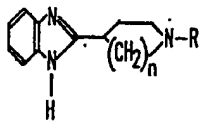
(19)

(54) 2-SUBSTITUTED BENZIMIDAZOLES

(71) We, A. H. ROBINS COMPANY, INCORPORATED, a Corporation organised and existing under the Laws of the State of Virginia, United States of America, of 1407 Cummings Drive, Richmond, Virginia 23220, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to 2-substituted benzimidazoles and provides certain novel compounds of this type, processes for preparing them, compositions containing them and methods of using such compounds and compositions.

The compounds according to the invention have the formula:



Formula I

wherein R represents lower-alkyl, phenyl, phenoxy-lower-alkyl, lower-alkoxy-phenoxy-lower-alkyl or 1,4-benzodioxan-2-ylmethyl; and *n* is 1 or 2. The invention also embraces acid addition salts of the compounds of Formula I.

As used herein, the following terms have the meanings indicated.

The term "lower-alkyl" means straight or branched chained alkyl radicals of up to eight carbon atoms inclusive. "Lower-alkoxy" has the formula -O-lower-alkyl.

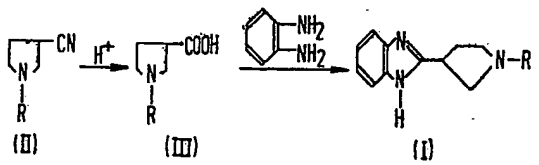
The compounds (including acid addition salts) of the invention generally exhibit pharmacological activity, in particular as analgetics and tranquilizers. The analgetic and tranquilizing activity of the compounds was determined by standard laboratory procedures which indicate that when compounds are tested under such procedures the results show the compounds to be active as analgetics and tranquilizers. In particular, the compounds of Formula I, wherein *n* is 1, namely 2-(1-substituted-3-pyrrolidinyl)-benzimidazoles, e.g. 2-(1-lower-alkyl-3-pyrrolidinyl)benzimidazoles, are analgetics while compounds of Formula I, wherein *n* is 2, namely 2-(1-substituted-4-piperidinyl)benzimidazoles, are tranquilizers. The analgetic activity was determined by the method of P. Nilsen, Acta. Pharmacol. Toxicol. *18*, 10 (1961). The tranquilizing activity was determined by the method of DaVanzo, J. P. et al., Psychopharmacologia 9, 210 (1966).

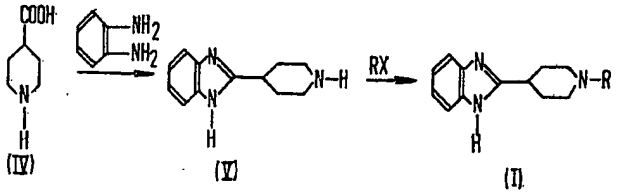
Useful acid addition salts may be derived from mineral acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, nitric acid, sulphuric acid, and phosphoric acid; and organic acids such as citric acid, lactic acid, fumaric acid, maleic acid, and tartaric acid. The preferred acid addition salt is hydrochloride.

The acid addition salts may be prepared either by dissolving the free base in an aqueous solution containing the appropriate acid and isolating the salt by evaporating the solution, or by reacting the free base and the selected acid in an organic solvent, in which case the salt ordinarily separates directly or can be recovered by concentration of the solution or other conventional methods. Conversely, the free base may be obtained by neutralizing the acid addition salt with an appropriate base such as

ammonia, ammonium hydroxide or sodium carbonate, extracting the liberated base with a suitable solvent, e.g. ethyl acetate or benzene, drying the extract and evaporating to dryness or fractionally distilling, or in some other conventional manner.

The process of producing the novel compounds of the present invention can be represented as follows:





wherein R and n are as defined above and X is halogen or $—N(CH_3)_2$.

A 1—R—3 cyanopyrrolidine of Formula II may be prepared as described in U.S. Patent 3,318,908. It may be dissolved in concentrated mineral acid, illustratively hydrochloric acid, and the acidic solution stirred at a temperature in the range of about 20°C. to about the reflux temperature for a period of from about two to about four hours. Generally, a concentration of about one gram of the cyanopyrrolidine to about five millilitres of the selected mineral acid is satisfactory. A solution of *o*-phenylenediamine in the same dilute mineral acid is added to the mixture and the resulting reaction mixture is stirred at reflux temperature for a period of from about 10 to about 80 hours; a blanket of an inert gas, for example, nitrogen, can be employed. The reaction mixture is cooled, the acidic solution basified using a dilute aqueous alkali solution or concentrated ammonium hydroxide to precipitate the novel compound of Formula I. The product is collected by suction filtration and the product is recrystallized from a suitable solvent or solvent system.

In a procedure for preparing the novel compounds of Formula I, wherein n is 2, a heterocyclic carboxylic acid of Formula IV, illustratively isonipecotic acid, and an equivalent quantity of *o*-phenylenediamine is refluxed in a suitable dilute mineral acid solution, for example, dilute hydrochloric acid, for a period of from about 10 to about 80 hours. The cooled acidic mixture is made basic using a dilute aqueous alkali solution or concentrated ammonium hydroxide which causes precipitation of the crystalline product corresponding to Formula V. The crude crystalline product is collected by filtration and crystallized from a suitable solvent or solvent system to give the compound V.

The compound having Formula V prepared by the method described immediately above is especially useful in preparing compounds within the scope of Formula I. Thus, the hydrogen atom of the secondary amine group of the piperidine nucleus exhibits all the reactive properties of the secondary amino group and enters readily into conventional displacement reactions with a variety of reactive compounds, including, for example, alkyl halides.

Generally speaking, a compound of Formula V prepared as described above is reacted with a compound containing a reactive halogen atom in a lower alkanol solvent, illustratively ethanol, containing an alkali metal salt, for example, sodium carbonate, as an acid binder. The reaction is preferably carried out at reflux temperature of the solvent employed, and following the reaction period water is added to the reaction mixture and the product is extracted into an organic solvent, preferably benzene. After washing and drying the organic solution, the solvent is evaporated and the product present in the residue is purified by crystallization. Alternately, the product, which sometimes precipitates as a crystalline solid when water is added to the cooled reaction mixture, is collected by suction filtration is further purified by crystallization.

The following Preparation 1 illustrates the preparation of an intermediate used as the starting material in Examples 2 to 4. The Examples illustrate the preparation of certain compounds according to the invention.

Preparation 1

2-(4-Piperidinyl)benzimidazole.

A solution of 10.8 g. (0.1 mole) of *o*-phenylenediamine, 12.9 g. (0.1 mole) of isonipecotic acid and 80 ml. of 6N hydrochloric acid was refluxed 16 hours, cooled and the solution made basic using concentrated ammonium hydroxide. The crystalline product which separated was collected by filtration and dried. The crude compound was dissolved in a hot benzene-isopropanol mixture, charcoal added, the solution filtered and the filtrate treated with isooctane. The white product which crystallized weighed 9.2 g. (46% yield) and melted with decomposition at 238—240°C.

Example 1

2-(1-Ethyl-3-pyrrolidinyl)benzimidazole.

A solution of 1-ethyl-3-cyanopyrrolidine (24.8 g., 0.20 mole) in 162 g. of concentrated hydrochloric acid was refluxed four hours and then a solution of *o*-phenylenediamine (16.2 g., 0.15 mole) in 250 ml. of 5% hydrochloric acid was added to the reaction mixture. The mixture was refluxed 16 hours, cooled and made basic with concentrated ammonium hydroxide. The product which separated from the aqueous basic solution was collected by filtration and recrystallized from a water-methanol mixture. The compound weighed 10 g. (34% yield) and melted at 184—186°C. After recrystallization from the same solvent system the product (the title compound) melted at 186—187°C.

Analysis:

Calculated for $C_{12}H_{17}N_3$:	C, 72.52;	H, 7.96;	N, 19.52
Found:	C, 72.55;	H, 7.91;	N, 19.62

Pharmacology: The analgetic ED_{50} in mice was calculated to be 14.5 mg./kg. intraperitoneally from the pharmacological data obtained using the Standard Test procedure of Nilsen.

Example 2

2-{1-[2-(*o*-Methoxyphenoxy)ethyl]-4-piperidinyl}benzimidazole.

A mixture of 10.1 g. (0.05 mole) of 2-(4-piperidinyl)benzimidazole, 11.6 g. (0.05 mole) of 2-*o*-methoxyphenoxy)ethylbromide, 20 g. of potassium carbonate and 100 ml. of ethanol was refluxed for 60 hours. The suspension was cooled, 200 ml. of water added and the mixture extrated with benzene. The benzene solution was concentrated and the residue recrystallized several times from a benzene-isopropyl ether mixture. The white title compound weighed 8.2 g. (46% yield) and melted with decomposition at 202—204°C.

Analysis:

Calculated for $C_{21}H_{25}N_3O_2$:	C, 71.77;	H, 7.17;	N, 11.96
Found:	C, 71.91;	H, 7.08;	N, 12.00

Example 3

2-[1-(1,4-Benzodioxan-2-ylmethyl)-4-piperidinyl]benzimidazole.

A mixture of 10.1 g. (0.05 mole) of 2-(4-piperidinyl)benzimidazole, 9.2 g. (0.05 mole) of 2-chloromethyl-1,4-benzodioxane, 20 g. of potassium carbonate and 100 ml. of 2-butanol was refluxed 72 hours. After the suspension was cooled and filtered, the filtrate was concentrated at reduced pressure. A hot methanol-water solution of the residue was treated with charcoal and filtered. The product which separated from the cooled filtrate melted at 196—200°C. and weighed 7.2 g. (41% yield). The pure title compound melted at 204—206°C. after it was recrystallized from a benzene-isooctane mixture.

Analysis:

Calculated for $C_{21}H_{23}N_3O_2$:	C, 72.18;	H, 6.63;	N, 12.03
Found:	C, 72.20;	H, 6.58;	N, 12.11

Example 4

2-[1-(2-Phenoxyethyl)-4-piperidinyl]benzimidazole.

A mixture of 10.1 g. (0.05 mole) of 2-(4-piperidinyl)benzimidazole, 10.1 g. (0.05 mole) of 2-phenoxyethyl bromide, 20 g. of potassium carbonate, and 100 ml. of ethanol was refluxed 16 hours. The cooled mixture was treated with 100 ml. of water. The white solid which separated was recrystallized initially from methanol-water and finally

from benzene-isooctane. The title compound which weighed 9.2 g. (57% yield) softened at ca. 210°C. and melted with decomposition at 214—216°C.

Analysis:

Calculated for $C_{20}H_{23}N_3O$:	C, 74.74;	H, 7.21;	N, 13.07
Found:	C, 74.81;	H, 7.35;	N, 13.16

The compounds according to the invention may be associated with a pharmaceutical carrier or excipient to form pharmaceutical compositions. The compounds are thus presented in a form suitable for oral or parenteral administration. Thus, for example, compositions for oral administration are solid or liquid and can take the form of capsules, tablets, coated tablets or suspensions employing carriers or excipients conveniently used in the pharmaceutical art. Suitable tableting excipients include lactose, potato and maize starches, talc, gelatin and stearic and salicylic acids, magnesium stearate, and polyvinylpyrrolidone.

For parenteral administration the carrier or excipient can be a sterile, parenterally acceptable liquid, e.g., water, or a parenterally acceptable oil, e.g., arachis oil, contained in ampoules.

Although very small quantities of the active materials of the present invention are effective when minor therapy is involved or in cases of administration to subjects having a relatively low body weight, unit dosages are usually five milligrams or above, and preferably 25, 50, or 100 milligrams or even higher, depending, of course, upon the emergency of the situation and the particular result desired. Five to 50 milligrams appear optimum per unit dose, while usual broader ranges appear to be one to 500 milligrams per unit dose. The active agents of the invention may be combined with other pharmacological active agents, or with buffers or antacids, for administration and the proportion of the active agent in the composition may be varied widely. It is only necessary that the active ingredient constitutes an effective amount, i.e., such that a suitable effective dosage will be obtained consistent with the dosage form employed.

Examples of compositions are given as follows.

Example Formulations

(1) Capsules

Capsules of 5 mg., 25 mg., and 50 mg. of active ingredient per capsule are prepared.

Typical blend for encapsulation:	Per Capsule, mg.
Active ingredient, as salt	5.0
Lactose	295.7
Starch	129.0
Magnesium stearate	4.3
Total	435.0

Uniformly blend the selected active ingredient with lactose, starch and magnesium stearate and encapsulate the blend.

(2) Tablets

A typical formulation for a tablet containing 5.0 mg. of active ingredient per tablet follows. The formulation may be used for other strengths of active ingredient by adjustment of weight of dicalcium phosphate.

		Per Tablet, mg.
(1)	Active ingredient, as salt	5.0
(2)	Corn starch	13.6
(3)	Corn starch (paste)	3.4
(4)	Lactose	79.2
(5)	Dicalcium phosphate	68.0
(6)	Calcium stearate	0.9
	Total	170.1

Uniformly blend (1), (2), (4), and (5). Prepare (3) as a 10% paste in water. Granulate the blend with starch paste and pass the wet mass through an eight mesh screen. The wet granulation is dried and sized through a twelve mesh screen. The dried granules are blended with the calcium stearate and compressed.

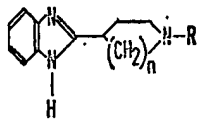
(3) Injectable—2% sterile solution

		Per cc.
Active ingredient	mg.	20
Preservative, e.g., chlorobutanol	percent wt./vol.	0.5
Water for injection		q.s.

Prepare solution, clarify by filtration, fill into vials, seal, and autoclave.

WHAT WE CLAIM IS:—

1. Compounds of the formula:



wherein R represents lower-alkyl, phenyl, phenoxy-lower-alkyl, lower-alkoxy-phenoxy-lower-alkyl or 1,4-benzodioxan-2-ylmethyl; and *n* is 1 or 2.

2. 2-(1-Lower-alkyl-3-pyrrolidinyl)benzimidazoles.

3. 2-(1-Ethyl-3-pyrrolidinyl)benzimidazole.

4. 2-{1-[2-(*o*-Methoxyphenoxy)ethyl]-4-piperidinyl}benzimidazole.

5. 2-[1-(1,4-Benzodioxan-2-ylmethyl)-4-piperidinyl]benzimidazole.

6. 2-[1-(2-Phenoxyethyl)-4-piperidinyl]benzimidazole.

7. Acid addition salts of compounds as claimed in any of the preceding claims.

8. A process for the preparation of compounds as claimed in Claim 1 which comprises the steps of:

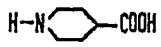
(1) hydrolyzing a heterocyclic compound of the formula

wherein R is as defined in Claim 1; and

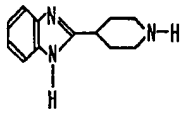
(2) condensing the heterocyclic carboxylic acid prepared in step (1) with *o*-phenylene diamine.

9. A process for the preparation of compounds as claimed in Claim 1 which comprises the steps of

(1) condensing *o*-phenylene diamine with a heterocyclic carboxylic acid of the formula



to give a compound of the formula



(2) alkylating the compound prepared in step (1) with a compound having the formula RX wherein R is as defined in Claim 1 and X is a halogen or the dimethylamino radical.

10. A process for preparing compounds as claimed in Claim 1 and acid addition salts thereof, substantially as described in any of Examples 1 to 4.

11. Compounds according to Claim 1 which have been prepared by a process as claimed in any of Claims 8 to 10.

12. A pharmaceutical composition in unit dosage form and useful for its analgetic effect, comprising (a) from 1 to 500 milligrams of a compound (or non-toxic acid addition salt thereof) as claimed in any of Claims 1 to 7 or 11, and (b) a pharmaceutically acceptable carrier therefor.

KILBURN & STRODE,
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